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Echinacea in the treatment and prevention of upper respiratory tract infections

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Introduction

An estimated $21.2 billion was spent on complementary medicine in 1997.[1] Echinacea, the top-selling herbal product in the United States, is at the forefront of the herbal revolution, with annual sales estimated at more than $300 million. The German Commission E lists that echinacea preparations "support and promote the natural powers of resistance of the body, especially in infectious conditions of the nose and throat."[2]

The objective of this analysis is to describe the pharmacology and clinical evidence for echinacea in the treatment and prevention of upper respiratory tract infections.

Historical use

Extracts, teas, tinctures, tonics, tablets, and ointments containing various parts of the echinacea plant (family Compositae) have been used since the 1600s by Native Americans. Tribes including the Cheyenne and the Crow used echinacea for a variety of medical problems, from sore gums and coughs to bowel trouble and snakebites.[3] The popularity of echinacea as a general medical treatment did not occur until the late 1800s, when Nebraska physician H.C.F. Meyer sold a root extract of *Echinacea angustifolia* as a "blood purifier."[4,5] Meyer subsequently sent his herbal concoction to John King and John Lloyd, a prominent physician/pharmacist team involved in the eclectic medicine movement of the late 1800s. Soon Lloyd Brothers Pharmacists of Cincinnati began marketing echinacea extracts as "anti-infective agents."[3-5] The popularity of echinacea extracts remained steady through the early part of this century, and from 1916 to 1950 echinacea was included in the US National Formulary. In the 1930s, with the advent of the sulfa antibiotics, the popularity of echinacea as an anti-infective agent began to wane in the United States, and only in the past few decades has it made a comeback.

Recent clinical studies of echinacea have focused on the treatment and prevention of upper respiratory infections. Other suggested uses include alleviation or reduction of adverse effects of chemotherapeutic agents; treatment of urinary tract infections; and topical use for chronic wounds, snake and mosquito bites, and recurrent *Candida* infections.[6]

Botany and taxonomy

The word "echinacea" is derived from the Greek *echinos,* meaning "hedgehog" or "sea urchin." The name was given to the plant because of its spiky seed heads.[4] The three most common echinacea species for medicinal purposes are *E angustifolia* (narrow-leaved), *E purpurea* (common), and *E pallida* (pale). *E purpurea* is the most popular commercially cultivated species. Common names for these perennial herbs include purple coneflower, Missouri snakeroot, Indianhead, scurvy root, comb flower, hedgehog, and red sunflower.[3-7] Native to Kansas, Nebraska, and Missouri, echinacea is closely related to sunflowers, daisies, and ragweed, all members of the Compositae/Asteraceae family. The stems have a sharp tingling taste when chewed.[8] Medicinal products are prepared from the dried roots of *E angustifolia* and *E pallida,* and from the juice of the stems and flowers as well as the root of *E purpurea.*[3,6,7]

Chemistry and pharmacology

As with many medicinal plants, echinacea contains at least six distinct chemical constituents with pharmacologic activity (polysaccharides, flavonoids, chicoric acid glycosides, essential oils, polyacetylenes, and alkylamides).[3-7] There is much controversy and confusion over which

chemicals present in echinacea are responsible for its activity. The three main species differ slightly in composition, and other factors such as the method of extraction, the time of year of harvest, and the part of the plant used can significantly affect the quantity of active ingredient(s) present.[4,5,7] The polysaccharide, alkylamide, and chicoric acid glycoside components are believed to provide most of echinacea's nonspecific immunostimulatory activity.

A number of polysaccharides with pharmacologic effects on the immune system have been isolated. Heteroxylan is a high-molecular-weight polysaccharide that activates phagocytosis. Arabinogalactan functions to promote the release of tumor necrosis factor and increases production of macrophage interleukin-1 and interferon beta-2.[6,8,9] Alkylamides and chicoric acid glycosides also appear to stimulate phagocytosis. Echinacein is an isobutylamide that is responsible for echinacea's pungent smell and distinct taste.[8,9]

While echinacea does not appear to have any direct antibacterial or antiviral activity, it appears to exert beneficial effects through immune system modulation, thus indirectly providing an "anti-infective" effect. Most studies investigating the pharmacology of echinacea have used the parenteral formulation, which is not available in the United States, and it is unclear to what degree the activity of the orally administered preparations mimics that of the parenteral formulation.[4,10]

Efficacy

Two systematic reviews have attempted to provide a clear description of the available literature.[11,12] Prior to these reviews, most echinacea clinical trials were in German, and not readily accessible. The first systematic review of clinical trials addressing echinacea's effects on immunomodulation evaluated a total of 26 clinical trials. Of those, only six used products containing echinacea as a sole component of the tested extract, and only three addressed the use of echinacea in the treatment or prevention of upper respiratory tract infections.[11,14,15] Recently two clinical trials investigating the use of echinacea in the prevention of upper respiratory infections were published in English.[13,14]

Braunig et al. conducted the two studies evaluating echinacea in the treatment of acute respiratory tract infections.[11,15,16] The first randomized controlled trial investigated the efficacy on reduction of length of illness of *E pallida* root extract 900 mg (90 drops) daily for 8 to 10 days versus placebo in a total of 160 patients with acute upper respiratory tract infection.[11,16] Patients treated with the echinacea extract had a significantly shorter duration of illness (13 vs 9.8 days, P<0.001). The second trial evaluated the use of *E purpurea* root extract at two different doses (450 mg [90 drops] or 900 mg [180 drops]) with placebo in 180 patients.[11,15] Patients taking the higher dose of extract fared significantly better than the placebo and low-dose groups in terms of cold symptoms evaluated at 3 to 4 and 8 to 10 days (P<0.0001). This study suggests the effects of echinacea in the treatment of upper respiratory tract infections are dose-dependent. It is unclear in the review of each of these trials if the treatment and placebo were initiated at the same point in the course of the acute upper respiratory tract infections in all patients.[11]

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Echinacea

The prevention trial conducted by Schoneberger et al. evaluated the use of pressed juice of *E purpurea* at a dose of 4 ml twice daily for 8 weeks versus placebo in 108 patients with a history of more than three upper respiratory infections in the previous six months.[11,17] The treatment group had a nonsignificant decrease in number and length of subsequent upper respiratory infections when compared with the placebo group.

Studies of echinacea in the prevention of upper respiratory tract infections have been published in the past year in English-language journals.[13,14] Melchart and colleagues evaluated the use of 50 drops of ethanolic extracts of *E purpurea* and *E angustifolia* root or placebo given twice daily for five days each week for 12 weeks in a three-armed randomized double-blind trial in 289 patients.[13] The primary outcome measure was the time taken to develop an upper respiratory tract infection. In the intent-to-treat analysis, no significant differences were found between the three groups in the mean number of days to the development of an upper respiratory tract infection, the percentage of patients with one or more infections, and the number of participants reporting adverse effects. The only significant result was that more patients in the two echinacea groups believed they had received benefit from their treatment (P=0.04), possibly due to problems with blinding the echinacea extracts. This study did not report concurrent use of echinacea in other forms or other pharmacologic agents (allopathic and complementary) that may potentially have an impact on the incidence and/or severity of upper respiratory tract infections. It is also nearly impossible to blind patients to the echinacea extracts due to their characteristic taste. Overall, limitations present in the available clinical trials include the different doses and different species of echinacea used in

each trial, different methods of extraction used in preparation of the tested medicinals, relative lack of standardization of initial diagnosis of upper respiratory tract infection, and frequent use of combination products.

The most recent prevention study was conducted by Grimm et al. in patients with a history of more than three colds or respiratory infections in the preceding year.[14] One hundred nine patients were randomly assigned to take either 4 ml fluid extract of *E purpurea* (from the whole flowering plant without roots and containing 22% alcohol) or 4 ml of alcohol/water solution twice a day for 8 weeks. There was not a significant difference between groups in terms of the incidence, duration, or severity of upper respiratory tract infections.

Safety and tolerability

Detailed assessments of adverse effects of herbal products are often not reported in clinical trials. Such is the case with many echinacea clinical studies. The German Commission E monographs state there are no known side effects with the oral and topical use of these agents.[2] Parenteral use has resulted in fever, elevations in white blood cell counts and blood glucose, nausea, and vomiting.[2] Adverse events detailed in the Grimm trial included mild and transient central nervous system and gastrointestinal effects that occurred at similar rates in the treatment and placebo groups.[14] Similar numbers of patients in each group withdrew from the study, most commonly because of the poor taste of the study medication and gastrointestinal effects. A similar adverse event and withdrawal pattern was seen in the Melchart et al. trial.[13]

A theoretical concern exists for cross-sensitivity of echinacea in those patients allergic to other members of the Compositae/Asteraceae family. A single case of echinacea-associated anaphylaxis (chest tightness, burning of the mouth and throat, and generalized urticaria) has been reported in the literature, in a woman with a history of multiple food and plant allergies.[18] Subsequent skin testing revealed allergy to echinacea extract and ragweed. Patients with known allergy to these plants (including daisies, sunflowers, and ragweed) should be cautioned regarding the use of echinacea products.

Echinacea does contain small amounts of pyrrozolidine alkaloids, but concern regarding pyrrozolidine-associated hepatotoxicity is not warranted, due to structural differences in these alkaloids that render them nontoxic compared with other known hepatotoxic pyrrozolidine alkaloids.[5,19] A general recommendation against the use of herbal products in patients with poor hepatic and/or renal function would be prudent, given the lack of safety information regarding use by these populations.

Combining echinacea products with known immunosuppressants should be avoided if possible, due to the possibility of a significant pharmacodynamic drug interaction.[19] The German Commission E states that the use of echinacea should be avoided in patients with any "progressive systemic immune disease" such as lupus, HIV infection or AIDS, or multiple sclerosis and in patients who have undergone organ transplantation or who are on immunosuppressants.[2] The use of echinacea should also be avoided in pregnant and lactating women until more information is available.[2] Echinacea should not be taken orally for more than 8 weeks because of the potential for decreased immune response with continuous use.[2]

Price

The cost of single-agent echinacea preparations varies widely, depending on manufacturer, echinacea content, species of echinacea, and dosage form. Capsules range from five to 75 cents apiece, liquid extracts from 25 to 35 cents per milliliter.[20]

Recommendations for clinical practice

Although echinacea appears to be safe in most patients, more clinical studies are needed to assess its efficacy. As evidenced by the studies detailed in the preceding section, the appropriate dose and most effective formulation of echinacea are not known. The German Commission E recommends 900 mg of *E pallida* root, or 6 to 9 ml of expressed juice of *E purpurea* herb.[2] For acute infections, a dose of 300 to 400 mg of a dry extract three times daily has been advocated.[3]

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